International Scholars Journals

International Journal of Obstetrics and Gynecology ISSN 2326-7234 Vol. 6 (1), pp. 200-206, January, 2018. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Which is more effective sildenafil citrate therapy or transdermal nitroglycerin in management of intrauterine growth restriction

Shahinaz H.El-Shorbagy[1], Abd-el ghaffar Dawood[1] and Abeer Elshabacy[2]

Obstetrics & Gynecology Department, Faculty of Medicine; Tanta University, Egypt[1]
Fellow of Obstetrics & Gynecology; Benha Teaching Hospital, Egypt[2]

Accepted 25 December, 2017

Intrauterine growth restriction (IUGR) is the failure of fetuses to achieve their full growth potential, and is a major cause of perinatal mortality and morbidity. The etiology of IUGR is multifactorial and is thought to include a combination of maternal, environmental, fetal and placental factors with a resultant decrease in fetal growth. Sildenafil citrate and transdermal nitroglycerin affect uteroplacental blood flow and potentiate fetal growth. The objective of this study is to evaluate the effects of sildenafil citrate (SC) and transdermal nitroglycerin (GTN) in management of intrauterine growth restriction. Fifty patients' singleton pregnancies (gestational age, 22–34 weeks) with IUGR in the present study were subjected to; complete history taking; clinical and blood pressure evaluation. Ultrasonographic examination was done every 2 weeks including fetal biometry: Biparietal Diameter "BPD", Head Circumference "HC", Abdominal Circumference "AC", HC/AC ratio, Femur Length "FL", Estimated Fetal Weight "EFW" to monitor fetal growth and assessment of biophysical profile. We compared every week mean arterial blood pressure (MAP) with Doppler ultrasound of the uterine (UtA), umbilical (UA) and fetal middle cerebral (MCA) arteries in pregnancies with IUGR before and after the use of 20 mg sildenafil citrate oral tablets twice daily or after application of a transdermal GTN (Novartis Ireland Limited) 5mg patch/day. Statistical analysis was performed by ANOVA for paired samples. The use of sildenafil citrate or transdermal GTN in pregnancies with IUGR is associated with non significant difference (>0.05) in demographic data, clinical characteristics and baseline values of fetal biometry in the two treated groups of IUGR. There was a significant reduction in PI, RI waveforms of UtA and UA arteries and MAP in pregnancies with IUGR after administration of either SC or GTN therapy. No significant change in MCA Doppler was observed in both groups. IUGR patients treated by either SC or GTN showed significant reduction in both UtA and UA Doppler wave (PI&RI) as well as MAP, with no effect on MCA Doppler wave (PI&RI). Therapy with either Sildenafil citrate or GTN improves uteroplacental (uterine arteries) and fetoplacental (umbilical arteries) circulation and potentiates fetal growth. Sildenafil citrate could normalize the uteroplacental insufficiency with a favorable fetal outcome better than GTN. Sildenafil citrate could be suggested as first line of the treatments for IUGR patients as it is cheaper, has less maternal or fetal complications.

Keywords: Sildenafil citrate, transdermal GTN, IUGR, EFW, gestational age, Doppler ultrasound.

INTRODUCTION

Intrauterine growth restriction (IUGR) is the failure of fetuses to achieve their full growth potential. Currently, between 5 and 10% of human infants undergo IUGR (1). Diagnosis of IUGR is based on femur length; head circumference, biparietal diameter, and abdominal circumference up to 28 weeks gestation (2). After 20 weeks, the BPD may diverge from the correct gestational age by 12–15 days, extending to 21 days after 30–32 weeks

Corresponding author's E-mail: shahyshorbagy70@yahoo.com

gestation. Because of this discrepancy, femur length is frequently chosen as a dependable indicator of gestational age in late pregnancy (3). Estimated fetal weight is calculated using polynomial equations combing BPD, femur length, and the abdominal circumference. The most common formulas are those reported by Hadloc et al [(4)]. Using these formula, IUGR is typically defined as estimated fetal weight less than the10th, 5th, or 3rd percentile for the gestational age or below2 standard devotions' of the mean for gestational age (5).

The most common etiology for IUGR is abnormal placentation, which is frequently associated with impaired placental blood flow causing inadequate maternal-fetal circulation, with a resultant decrease in fetal growth (6).

Thus, research has been focused on devising preventive and therapeutic strategies for IUGR and, specifically, on developing therapies to improve placental development and utero–placental blood flow (7).

In a normal pregnancy, the trophoblast produces nitric oxide (NO) which plays an important role in vasodilatation in the feto-placental circulation to improve oxygen and nutritional supply to the fetus (8). In complicated pregnancy by pre-eclampsia or IUGR, inflammation caused placental hypoxia and endothelial dysfunction associated with decreased release of NO and increased phosphodiesterase type 5 (PDE-5) activity (9).

Nitric oxide relaxes vascular smooth muscle through a cGMF-mediated pathway and NO synthase isoforms have been identified in the uterus. Sildenafil citrate (Viagra), a type 5-specific phosphodiesterase inhibitor, augments the vasodilatory effects of NO on vascular smooth muscle by preventing the degradation of cGMP (10,11). Sildenafil citrate is considered a potential agent in treating pregnant women with intrauterine growth restriction or as a tocolytic agent helping maintenance of pregnancy (12,13).

Different studies in rodent models have demonstrated that SC administration during pregnancy prevents the production of inflammatory cytokines, prevents fetal loss (14), improves feto–placental blood flow and increases fetal weight (15,16).

Glyceryl trinitrate (nitroglycerin, GTN) produces NO through a biotransformation pathway and improved Doppler indices and maternal blood pressure. However, some of its limitations are the development of tolerance and headache which can be reduced by intermittent administration (17, 18).

The objective of this study was to evaluate the effects of SC versus transdermal GTN on management of intrauterine growth restriction.

PATIENTS AND METHODS

This was a prospective study conducted at Tanta university Hospital from November 2014 to January 2016, after research ethical committee approval and written informed consent was taken from all patients included in this study (2912/12/14).

The Study included fifty women with singleton pregnancy suffering from IUGR diagnosed by either lag of two weeks or more between the current biometric measures and the documented pregnancy dating in the first trimester or estimated fetal weight less than the 10th percentile for gestational age. The inclusion criteria were: age range between 20 -38 years; singleton pregnancy with IUGR; gestational age between 22 - 34weeks; body mass index (BMI) $\leq$ 30 kg/m2; intact membranes. The exclusion criteria were: Subject refusal; women with twin pregnancy; women suffering from anemia; diabetes mellitus; previous hypertension or other chronic diseases of kidney; urinary tract infection; chronic liver; cardio vascular disease and those who had fetal malformation; known aneuploidy; syndrome or congenital infection; known intolerance to sildenafil or GTN; serum creatinine >1.0mg/dL and fetal death.

Gestational age was calculated from the date of the last menstrual period and was confirmed by ultrasound examination performed in the first half of the pregnancy.

Body mass index was defined as maternal weight divided by maternal height squared (kg/m^2)(19).

Pregnant women with IUGR were randomly divided into two groups 25 each. Women of the first group received 20 mg sildenafil citrate oral tablets twice a day. Women of the second group had a 5mg transdermal GTN patch/day (Novartis Ireland Limited) applied to the abdominal skin. Sildenafil citrate and GTN doses were selected based on the safety profile from previous studies (18).

All women included in the study on time of hospital admission were subjected to; full history taking, general and obstetric examination, and laboratory investigations including blood grouping, Rh typing, complete blood count (CBC), blood urea, serum creatinine, liver function tests and complete urine analysis. Ultrasonographic examination was done including fetal biometry every 2 weeks: Biparietal Diameter "BPD", Head Circumference "HC", Abdominal Circumference "AC", HC/AC ratio, Femur Length "FL", Estimated Fetal Weight "EFW" to monitor fetal growth and assessment of biophysical profile.

Doppler velocimetry on uterine (UtA), umbilical (UA) and fetal middle cerebral arteries (MCA) were performed immediately before and one week after medication and repeated weekly till delivery. The examinations were performed using a Samsung ultrasound machine; model H60, USS- H60NF4K/WR (Samsung, Korea) with 3.5-MHz and 5-MHz convex probes was used. The high-pass filter was set at 100 Hz. The Doppler sample gate was adjusted according to vessel diameter, and the insonation angle was maintained as close to zero as possible. Pulsatility index (PI) and Resistive index (RI) were automatically calculated by the equipment. Examinations were carried out with the patients in the semi-Fowler position to avoid orthostatic hypotension. Scans of the

vessels were obtained during fetal inactivity, during periods of apnea and in the absence of uterine contractions.

The sequence in which the vessels were examined was uterine arteries followed by umbilical artery and then fetal MCA. Doppler flow velocimetry of the uterine arteries was performed according to the usual technique. Measurements were obtained from the ascending branches of the right and left UtAs at the point of apparent crossing with the external iliac arteries. For the umbilical artery, velocimetry was carried out on a free loop at the midpoint between the placental and abdominal insertions of the vessel, and for the MCA it was performed in an axial section of the brain at the level of the circle of Willis.

Maternal arterial blood pressure was measured using a sphygmomanometer (mercury column, always on the left arm, with the patient sitting and with the fourth Korotkoff sound used to determine diastolic blood pressure). Mean arterial blood pressure (diastolic pressure+1/3 (systolic pressure−diastolic pressure) was used for comparisons between studied groups (18). Finally, all data were entered into and stored in a database. The sonographically measured Doppler indices obtained were correlated with each other and statistically analyzed by ANOVA test (Analysis of Variance- version 17), where description of quantitative variables as range; mean and standard deviation (SD); description of qualitative variables as number and percentage were done and compared with MAP before and after administration of therapy.

RESULTS

Analysis was carried out on 50 women with singleton pregnancy suffering from IUGR divided into 2 equal groups. First group received 20 mg sildenafil citrate oral tablets twice a day and second group had a 5mg transdermal GTN/day applied to the abdominal skin. Table 1 summaries the Demographic data, clinical characteristics and baseline values in two groups of IUGR, showing no significant difference (>0.05).

There were no significant difference between both studied groups regarding rate of increase of BPD, HC, AC, FL, but significant increase in rate of EFW per 2 weeks was detected after SC compared to transdermal GTN (Table 2).

There was a significant decrease in the PI and RI of the uterine and umbilical arteries after using sildenafil or transdermal GTN, but no significant change was observed in the PI or the RI of MCA and in amniotic fluid index (AFI). Mean arterial blood pressure decreased significantly after administration of both sildenafil and transdermal GTN ($P<0.05$). When comparing the two study groups, there was no significant difference after administration of either sildenafil or transdermal GTN therapy (Table 3, Fig.).

There was no significant difference in GA at delivery between the two treated groups. In the present study sildenafil citrate showed more increase in birthweight of newborns than that in transdermal GTN treated group. No fetal tachycardia or bradycardia, or neonatal deaths in any of the studied groups, but neonatal complications and maternal adverse effects were more pronounced in transdermal GTN than in SC group. Headache was the most common side-effect met with during treatment with GTN (Table 4).

DISCUSSION

Fetal growth restriction (FGR) is the single most important contributor to perinatal mortality in non-anomalous fetuses (20). Significant research efforts have gone into improving the diagnosis and definition of IUGR, surveillance and antenatal management, however uncertainties regarding the optimal timing of delivery in IUGR persist (21).

Our study shows that sildenafil citrate and transdermal GTN application given to pregnant women with IUGR are effective in decreasing the resistance to blood flow in the uteroplacental (UtAs) and fetoplacental (UAs) circulations, as well as MAP, with no change in resistance to blood flow in the fetal cerebral circulation (MCA). Such finding coincided with those of Johal et al and Panda et al [22,23] . These drugs could be of beneficial use as antihypertensive drugs in cases of placental vascular insufficiency.

Sildenafil citrate is increasingly used in the pregnant patient for the treatment of pulmonary hypertension in pregnancy, a disease associated with poor maternal and fetal outcome (24). Its safety and efficacy in this setting, combined with its lack of teratogenic or feto-toxic effects even at very high dosages in animal studies, increase its use for the treatment of pulmonary hypertension in pregnancy, as well as cases of IUGR (25).

There is increased myometrial small artery vasoconstriction and decreased endothelium-ependent vasodilatation in vessels from women whose pregnancies are complicated by FGR. Sildenafil citrate significantly reduces vasoconstriction, improves relaxation of FGR small arteries, and improves endothelial function of myometrial vessels from women whose pregnancies are complicated by intrauterine growth restriction. Sildenafil citrate may offer a potential therapeutic strategy to improve uteroplacental blood flow in FGR pregnancies as previously reported by Wareing et al[26] . The vasodilator properties of sildenafil were important to us, as a decrease in maternal blood pressure without a concomitant increase in blood flow in the UtA could aggravate placental underperfusion.

Transdermal GTN application was similar to SC caused significant reduction in the RI and PI of the uterine and umbilical arteries, as well as of maternal blood pressure, without any effect on the RI and PI of the fetal middle

Table 1. Demographic data of the studied groups.

Data	Sildenafil Citrate (n=25)	Transdermal GTN (n=25)	P Value
Maternal age (years)			
Range	20-38	21-38	
(Mean±SD)	28.76±4.70	29.52 ± 4.97	0.635
Gravidity			
Range	0-5	0-4	0.077
(Mean±SD)	2.8±1.22	2.92±1.07	
Parity			
Range	0-4	0-4	
(Mean±SD)	1.72± 1.27	1.76± 1.2	0.828
Gestational age (weeks) at admission			
Range	22-34	24-34	0.328
(Mean±SD)	27.92±4.01	26.52±3.31	
Body mass index (kg/m^2)			
Range	18-30	20-30	
(Mean±SD)	24.56±4.15	25.16±3.06	0.252
Fetal weight at admission (g)			
Range	500-1880	650-1850	
(Mean±SD)	908.8± 327.71	994±276.78	0.991

GTN =Glyceryl trinitrate; n= number; SD= Standard deviation.

Table 2. Comparing both groups regarding rate of increase in BPD, HC, AC, FL, and rate of increase of EFW per 2 weeks.

Data (Mean±SD)	Sildenafil (n=25)	Transdermal GTN (n=25)	P. value
BPD/2W (mm)			
Range	3-8	3-8	
(Mean±SD)	5.4± 1.60	5.32± 1.65	0.698
HC/2W (mm)			
Range	5-22	6-21	
(Mean±SD)	14.36±5.46	14.08± 4.48	0.064
AC/2W (mm)			
Range	9-30	8-30	0.516
(Mean±SD)	19.28± 5.74	20.60± 4.91	
FL/2W (mm)			
Range	2-8	2-12	0.830
(Mean±SD)	5.04±1.48	5.36±2.25	
EFW/2W (g)			
Range	65-130	70-120	0.036*
(Mean±SD)	83.4±19.02	81.2±16.60	

GA= Gestational age; BPD = Biparietal Diameter; HC= Head Circumference; AC= Abdominal circumference; EFW= Estimated fetal weight.

cerebral artery. Such finding was similar to those of Trapani [18] Transdermal GTN produces nitric oxide (NO) through a biotransformation pathway (17). Nitric oxide plays an important role in vasodilatation in the feto-placental circulation to improve oxygen and nutritional supply to the fetus (27).

This study shows that sildenafil citrate and transdermal GTN application are effective in decreasing the resistance to blood flow in the uteroplacental and fetoplacental circulations, as well as mean maternal blood pressure in patients with IUGR with no change in resistance to blood flow in the fetal cerebral circulation (MCA). Such findings coincided with those of Luzi et al [28], indicating that the fetal cerebral arterial vascular tonus is not dependent on external nitric oxide supply. When fetal hypoxemia occurs, there is a decrease in cerebral vascular resistance as a defense mechanism (29). In the present study sildenafil citrate

Table 3. Comparison of PI and RI of Uterine, Umbilical, Middle cerebral arteries, MAP and AFI of the studied groups.

Parameter (Mean±SD)	SC (n=25)		Transdermal GTN (n=25)		P. correlation after SC vs.GTN
	Before	After	Before	After	
Ut A PI	1.38±0.23	0.93±0.24	1.43±0.25	0.91±0.24	0.920
P. value	0.035		0.021		
UtA RI	1.09±0.28	0.72±0.15	1.4±0.25	0.66±0.16	0.890
P. value	0.016		0.012		
UA PI	0.98±0.11	0.73±0.03	1.00±0.17	0.72±0.09	
P. value	0.019		0.053		0.896
UA RI	0.78±0.08	0.55±0.11	0.84±0.06	0.65±0.14	
P. value	0.052		0.048		0.692
MCA PI	1.64±0.11	1.65±0.15	1.72±0.09	1.67±0.08	
P. value	0.360		0.92		0.675
MCA RI	0.79 + 0.13	0.71±0.02	0,78±0.12	0.71±0.06	
P. value	0.532		0.219		0.861
MAP	120.4±6.71	108.2±1.68	125.4±4.01	103.81±6.40	
P. value	0.0037		0.023		0.931
AFI	6.38±1.04	7.24±1.16	6.14±1.48	6.44±0.93	0.360
P. value	0.074		0.805		

PI=pulsatility indices; RI= resistance indices; MAP =Maternal arterial blood pressure; AFI = amniotic fluid index; SC =Sildenafil citrate; GTN= Glyceryl trinitrate or nitroglycerin; vs. = versus

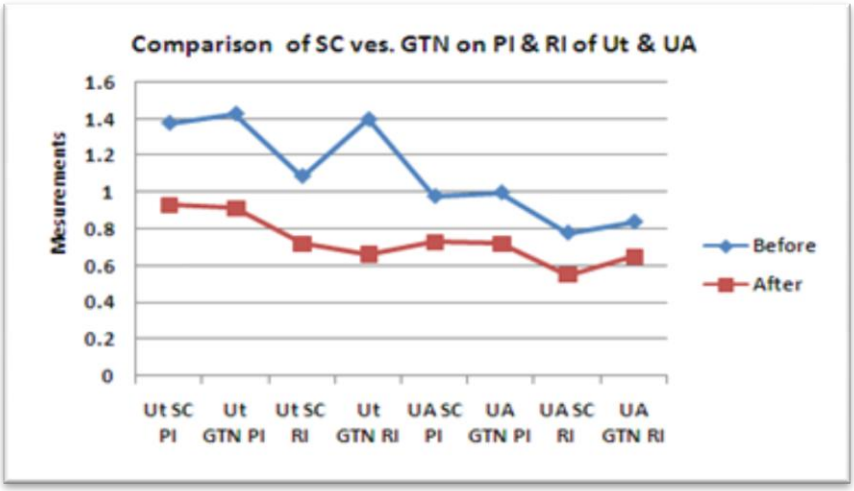

Fig. Comparison between the two study groups according to the mean Ut and UA (PI and RI).

showed more increase in fetal weight than that after the use of transdermal GTN patch and that coincided with the results of Bruschettini et al [30].

Fetal and maternal side effects were more pronounced after GTN administration than after SC and this could be the main limiting factor for use of GTN in clinical application. Headache was the most common side effect, observed in 32% of the patients receiving sildenafil citrate and in 56% of patients with a GTN patch. Similar results have been reported in other studies (31).

Despite a few negatives studies, sildenafil citrate has shown promise in vitro as well as in animal studies in the treatment of both IUGR (7), and pre-eclampsia (32).We have not performed a negative control to cases of IUGR in order not to bother and harm the patients by using placebo that were only for comparison and not treatment,

Table 4. Comparing both groups regarding gestational age at delivery, birthweight of newborns, fetal and maternal complications.

Data (Mean±SD)	Sildenafil (n=25)	Transdermal GTN (n=25)	P. value
GA at delivery (weeks)	35.2±0.83	32.4±2.6	0.368
Birthweight of newborns (g)	1848.89±175.460	1724.44± 281.341	0.207
Fetal complications (N.%)			
• **RD syndrome**	• 6 (24)	• 9 (36)	
• **Infection**	• -----	• 2(8)	
• **Hypotension**	• -----	• 2(8)	
• **Pneumothorax**	• 1(4)	• 1(4)	
• **Convulsion**	• ----	• 1(4)	
• **Intraventricular hemorrhage**	• 1(4)	• 3(12)	
Maternal complications (N.%)			
• **Headache**	• 8(32)	• 14 (56)	
• **Visual disturbances**	• 5 (20)	• 8(32)	
• **Epigastric pain**	• 5 (20)	• 6(24)	
• **Vomiting**	• 3(12)	• 4(16)	
• **Postpartum hemorrhage**	• -----	• 1(4)	

GA= Gestational age, RD syndrome= Respiratory distress syndrome.

as we used the parameters of cases before SC and transdermal GTN as the negative control.

Overall there does not appear to be any severe adverse maternal side effects nor any increase in the rate of neonatal anomalies after SC compared to GTN during management of IUGR. Further studies with larger sample size are needed to fully verify that Sildenafil citrate has a better therapeutic profile with fewer complications than that of GTN.

REFERENCES

1. Nardozza LM, Araujo Junior E, Barbosa M M, Caetano A C, Lee D J, and Moron AF: Fetal growth restriction: current knowledge to the general Obs/Gyn. Arch. Gynecol. Obstet, 2012; 286:1–13. doi:10.1007/S00404-012-2330-6
2. Mongelli M, Yuxin N G, Biswas A, and Chew S: Accuracy of ultrasound dating formulae in the late second-trimester in pregnancies conceived with in-vitro fertilization. Acta Radiologica, 2003; 44(4): 452–455.
3. Benson C B and Doubilet PM: Sonographic prediction of gestational age: accuracy of second- and third-trimester fetal measurements. American Journal of Roentgenology, 1991; 157(6): 1275–1277.
4. Hadlock FP, Harrist RB, and Sharman R S: Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study. American Journal of Obstetrics and Gynecology, 1985; 151(3): 333–337.
5. Blackwell SC, Moldenhauer J, Redman M, Hassan SS, Wolfe HM, and Berry SM: Relationship between the sonographic pattern of intrauterine growth restriction and acid-base status at the time of cordocentesis, Archives of Gynecology and Obstetrics, 2001; 264(4) : 191–193.
6. ACOG Practice bulletin no. 134: fetal growth restriction. American College of Obstetricians and Gynecologists. Obstet Gynecol, 2013; 121: 1122–1133.
7. Tello J Lo´pez, Lvarez M AA, Martınez MAJN, Ferna´ndez AB, Garcı´a RMG, Rodrı´guez M, Lorenzo PL, Rovira LT, Astiz S, Lez-Bulnes AG, and Rebollar PG: The effects of sildenafil citrate on feto–placental development and haemodynamics in a rabbit model of intrauterine growth restriction. Reproduction, Fertility and Development, 2016; 29 (6): 1239-1248. https://doi.org/10.1071/RD15330
8. Rosselli M, Keller RJ, and Dubey RK: Role of nitric oxide in the biology, physiology and pathophysiology of reproduction. Hum Reprod, Update, 1998; 4:3–24.
9. Miller SL, Loose JM, Jenkin G, and Wallace EM: The effects of sildenafil citrate (Viagra) on uterine blood flow and well being in the intrauterine growth-restricted fetus. Am J Obstet Gynecol, 2009; 200: 102.e1–7.
10. Sher G, and Fisch JD: Vaginal sildenafi l (Viagra): a preliminary report of a novel method to improve uterine artery blood flow and endometrial development in patients undergoing IVF. Hum Reprod, 2000; 15:806–809.
11. Martin D and Conrad KP: Expression of endothelial nitric oxide synthase by extravillous trophoblast cells in the human placenta. Placenta, 2000; 21:23–31.
12. Sher G, and Fisch JD: Effect of vaginal sildenafi l on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development. Fertil Steril, 2002; 78:1073–1076.
13. El-Far M, El-Motwally Ael G, Hashem IA, and Bakry N: Biochemical role of intravaginal sildenafi l citrate as a novel antiabortive agent in unexplained recurrent spontaneous miscarriage: first clinical study of four case reports from Egypt. Clin Chem Lab Med, 2009; 47:

1433–1438.
14. Luna RL, Nunes AK, Oliveira AG, Araujo S M, Lemos A J, Rocha S W, Croy B A, and Peixoto C A: Sildenafil (Viagra) blocks inflammatory injury in LPS-induced mouse abortion: a potential prophylactic treatment against acute pregnancy loss? Placenta, 2015; 36: 1122–1129. doi:10.1016/J.PLACENTA.2015.07.133
15. Stanley J L, Andersson I J, Poudel R, Rueda-Clausen C F, Sibley CP, Davidge S T, and Baker PN: Sildenafil citrate rescues fetal growth in the catechol-o-methyl transferase knockout mouse model. Hypertension, 2012; 59:1021–1028. doi:10.1161/HYPERTENSIONAHA. 111.186270
16. Dilworth M R, Andersson I, Renshall L J, Cowley E, Baker P, Greenwood S, Sibley C P, and Wareing M: Sildenafil citrate increases fetal weight in a mouse model of fetal growth restriction with a normal vascular phenotype. PLoS One,2013; 8, e77748. doi:10.1371/ JOURNAL.PONE.0077748
17. Hashimoto S, and Kobayashi A: Clinical pharmacokinetics and pharmacodynamics of glyceryl trinitrate and its metabolites. Clin Pharmacokinet, 2003; 42: 205–221.
18. Trapani A Jr, Gonc¸alves LF, and Pires MMS: Transdermal nitroglycerin in patients with severe pre-eclampsia with placental insufficiency: effect on uterine, umbilical and fetal middle cerebral artery resistance indices. Ultrasound Obstet Gynecol, 2011; 38: 389–394.
19. Kabiru W, and Raynor BD: Obstetric outcomes associated with increase in BMI category during pregnancy. Am J Obstet Gynecol, 2004; 191: 928–932.
20. Gardosi J, Madurasinghe V, Williams M, Malik A, and Francis A: Maternal and fetal risk factors for stillbirth: population based study. BMJ 2013;346: f108.
21. Unterscheider J, O'Donoghue K, Daly S, Geary MP, Kennelly MM, McAuliffe FM, Hunter A, Morrison JJ, Burke G, Patrick and Fergal D M: Fetal growth restriction and the risk of perinatal mortality–case studies from the multicentre PORTO study. Pregnancy and Childbirth, 2014; 14:63-69
22. Johal T, Lees CC, Everett TR, and Wilkinson IB: The nitric oxide pathway and possible therapeutic options in pre-eclampsia. Br J Clin Pharmacol, 2014; 78: 244–257.
23. Panda S, Das A, and Nowroz H: Sildenafil citrate in fetal growth restriction. J Reprod Infertil, 2014; 15: 168–169.
24. Warnes CA: Pregnancy and pulmonary hypertension. Int J Cardiol , 2004; 97: (Suppl 1):11-13.
25. Villanueva-Garcia D, Mota-Rojas D, Hernandez-Gonzalez R, Sanchez- Aparicio P, Alonso-Spilsbury M, Trujillo-Ortega ME, Necoechea RR, and Nava-Ocampo AA: A systematic review of experimental and clinical studies of sildenafil citrate for intrauterine growth restriction and pre-term labour. J Obstet Gynaecol , 2007; 27(3):255-259.
26. Wareing M, Myers JE, O'Hara M, and Baker PN: Sildenafil citrate (Viagra) enhances vasodilatation in fetal growth restriction. J Clin Endocrinol Metab, 2005; 90(5):2550-2555.
27. Rosselli M, Keller RJ, and Dubey RK. Role of nitric oxide in the biology, physiology and pathophysiology of reproduction. Hum Reprod Update, 1998; 4:3–24.
28. Luzi G, Caserta G, Iammarino G, Clerici G, and Di Renzo GC.: Nitric oxide donors in pregnancy: fetomaternal hemodynamic effects induced in mild preeclampsia and threatened preterm labor. Ultrasound Obstet Gynecol, 1999; 14: 101–109.
29. Baschat AA, and Gembruch U. The cerebroplacental Doppler ratio revisited. Ultrasound Obstet Gynecol, 2003; 21: 124–127.
30. Bruschettini M, Gazzolo D, and Di Lorio R: Marenal nitric oxid supplementation decreasw cord blood s100B IN IUGR clinical chemistry April 2002 vol.48 (4): 647-650
31. Samangaya RA, Mires G, Shennan A, Skillern L, Howe D, McLeod A, and Baker N: A randomised, double-blinded, placebo-controlled study of the phosphodiesterase type 5 inhibitor sildenafil for the treatment of preeclampsia. Hypertens Pregnancy, 2009; 28: 369–382.
32. George EM, Palei AC, Dent EA, and Granger JP: Sildenafil attenuates placental ischemia-induced hypertension. Am J Physiol Regul Integr Comp Physiol 2013; 305: R397–403.